Primary Antibody Deficiency in a Tertiary Referral Hospital: A 30-Year Experiment

Article *in* Journal of investigational allergology & clinical immunology: official organ of the International Association of Asthmology (INTERASMA) and Sociedad Latinoamericana de Alergia e Inmunología · December 2015

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ORIGINAL ARTICLE

Primary Antibody Deficiency in a Tertiary Referral Hospital: A 30-Year Experiment

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Abstract

Background: Primary antibody deficiency (PAD) is the most common group of primary immunodeficiency disorders (PID), with a broad spectrum of clinical features ranging from severe and recurrent infections to asymptomatic disease.
Objectives: The current study was performed to evaluate and compare demographic and clinical data in the most common types of PAD.
Materials and Methods: We performed a retrospective review of the medical records of all PAD patients with a confirmed diagnosis of common variable immunodeficiency (CVID), hyper IgM syndrome (HIgM), selective IgA deficiency (SIgAD), and X-linked agammaglobulinemia (XLA) who were diagnosed during the last 30 years at the Children's Medical Center, Tehran, Iran.
Results: A total number of 280 cases of PAD (125 CVID, 32 HIgM, 63 SIgAD, and 60 XLA) were enrolled in the study. The median (range) age at the onset of disease in CVID, HIgM, SIgAD, and XLA was 2 (0-46), 0.91 (0-9), 1 (0-26), and 1 (0-10) years, respectively. Gastrointestinal infections were more prevalent in CVID patients, as were central nervous system infections in XLA patients. Autoimmune complications were more prevalent in HIgM patients, malignancies in CVID patients, and allergies in SIgAD patients. The mortality rate for CVID, HIgM, and XLA was 27.2%, 28.1%, and 25%, respectively. No deaths were reported in SIgAD patients.
Conclusions: SIgAD patients had the best prognosis. While all PAD patients should be monitored for infectious complications, special attention should be paid to the finding of malignancy and autoimmune disorders in CVID and HIgM patients, respectively.

Key words: Common variable immunodeficiency. Immunoglobulin A deficiency. Infection. Hyper-IgM syndrome. X-linked agammaglobulinemia.

Resumen

Antecedentes: Las inmunodeficiencias humorales primarias (PAD) es el grupo más frecuente de inmunodeficiencias primarias (IDP), y engloba un amplio espectro de características clínicas, que van desde los pacientes con infecciones graves y recurrentes a los casos asintomáticos.
Objetivos: El presente estudio se realizó para evaluar y comparar los datos demográficos y clínicos de los tipos más comunes de PAD.
Materiales y Métodos: Se revisaron retrospectivamente, las historias clínicas de todos los pacientes con PAD con un diagnóstico confirmado de: inmunodeficiencia variable común (CVID), síndrome de hiper IgM (HIgM), deficiencia selectiva de IgA (SIgAD),y de agammaglobulinemia ligada al cromosoma X (XLA), que fueron diagnosticados durante los últimos 30 años, en el Centro Médico de Niños, Teherán, Irán.
Resultados: Se incluyeron en este estudio un total de 280 casos de PAD, englobando 125 pacientes con CVID, 32 HIgM, 63 SIgAD, y 60 pacientes con XLA. La mediana (rango) de edad al inicio de la enfermedad en la CVID, HIgM, SIgAD y XLA fue: 2 (0-46), 0,91 (0-9), 1 (0-26) y 1 (0-10) años, respectivamente. Las infecciones gastrointestinales fueron más frecuentes en los pacientes con CVID, mientras que las infecciones del sistema nervioso central lo fueron en la XLA. Las complicaciones autoinmunes fueron más prevalentes en los pacientes con HIgM, los tumores malignos en las CVID y las enfermedades alérgicas en las SIgAD. La tasa de mortalidad de CVID, HIgM y XLA fue 27,2%, 28,1% y 25%, respectivamente. No hubo mortalidad en el grupo de pacientes con SIgAD.
Conclusiones: Los pacientes con SIgAD tuvieron el mejor pronóstico. Aunque todos los pacientes con PAD deben ser controlados estrechamente para evitar las complicaciones infecciosas, se debe prestar especial atención a la aparición de enfermedades malignas y autoinmunes en los pacientes con CVID y HIgM, respectivamente.

Palabras clave: Inmunodeficiencia variable común. Deficiencia selectiva de inmunoglobulina A. Infección. Síndrome hiper IgM. Agammaglobulinemia ligada al cromosoma X.

Introduction

Primary antibody deficiency (PAD) is the most common group of primary immunodeficiency disorders (PID). It results from various defects in the development and function of the B-cell lineage [1]. The spectrum of PAD is broad, ranging from severely reduced serum Ig titers and totally absent B cells to selective antibody deficiency and normal serum Ig [2]. Hypogammaglobulinemia, or antibody deficiency, is the hallmark of PAD. Affected individuals share a clinical phenotype with common features such as chronic and recurrent infections, chronic inflammation, and autoimmunity [2], leading to recurrent hospitalization and impaired quality of life [3,4]. Patients with PAD also tend to develop malignancies and lymphoproliferative disorders [5,6].

PAD often arises as a result of defects in early B-cell development in bone marrow and class switch recombination (CSR) or terminal B-cell differentiation in secondary lymphoid organs [1,7]. Defects in early B-cell development in bone marrow result in agammaglobulinemia (X-linked or autosomal recessive), which is characterized by profound reduction in serum Ig, markedly reduced mature B cell counts in the peripheral circulation, and early onset of recurrent bacterial infections [8-11]. Defects in CSR result in low serum levels of IgG and IgA and normal or elevated levels of serum IgM. Recurrent bacterial infections are common in PAD patients with defects in CSR (hyper-IgM syndrome) [12,13]. Defects in several genes, including CD40 ligand (*CD40L*), CD40, inhibitor of κ light polypeptide gene enhancer in B-cells, kinase gamma (*IKBKG*), activation-induced cytidine deaminase (*AID*), and uracil N glycosylase (*UNG*) have been known to cause CSR defects [12]. Defects in terminal stages of B-cell development that are controlled by genetic signatures result in antibody deficiency with isolated Ig class deficiency, namely, selective IgA deficiency (SIgAD), or deficiency in all 3 Ig classes, namely, common variable immunodeficiency (CVID) [14,15]. SIgAD is the most common primary immunodeficiency in Caucasians [16-18], whereas CVID is the

most prevalent symptomatic PAD [19]. Although most cases of SIgAD are asymptomatic, symptomatic SIgAD shares many clinical features with CVID [20]. A common genetic basis for SIgAD and CVID has been suggested based on co-occurrence in members of the same family and on the similarity in the underlying B-cell defects. Progression from SIgAD to CVID has also been reported [20,21].

Demographic and clinical data have been reported for various types of PAD [22,23]. However, studies comparing these findings between various PAD types in the same clinical setting are lacking. Moreover, physicians' poor awareness of these disorders remains a major cause of morbidity and mortality in affected patients [24,25]. The current study was performed to evaluate and compare the demographic and clinical data of the most common types of PAD in patients who were diagnosed and treated in a tertiary referral hospital in Iran over a 30-year period.

Methods

Patient Selection

We reviewed the medical records of all patients diagnosed with PAD between March 1983 and March 2013 at the Children's Medical Center, Tehran, Iran. Patients with CVID, HIgM, SIgAD, and XLA were enrolled. Other types of PAD were excluded from the study because of low prevalence or clinical insignificance. PAD was diagnosed according to the criteria of the Pan-American Group for Immunodeficiency and the European Society for Immunodeficiencies [26]. Secondary causes of immunodeficiency were ruled out in all patients. The study was approved by the Ethics Committee of Tehran University of Medical Science. All patients or their legal guardians were asked to complete an informed consent form. Patients' names were replaced with codes before data entry.

Data Collection

Using patients' medical records, we completed a 2-page questionnaire to record demographic data, clinical manifestations, past medical history, immunologic findings, long-term follow-up, complications, and disease outcome. All questionnaires were then evaluated, and those with missing data were completed by the immunologist responsible for the patient's management. Finally, patient data were included in the study after the diagnosis of PAD was confirmed by another immunologist.

Laboratory Testing

Blood samples were tested for Ig levels and CD markers and compared with their normal quantitative range. Other laboratory tests included a complete blood count, isohemagglutinin titer, and Schick test. Measurements of B-cell and T-cell subsets of patients diagnosed before 1993 were repeated using flow cytometry, as the method used before 1993 was based on rosette formation. DNA mutation analysis was also performed in some cases. Paraclinical evaluations such as pulmonary function, high-resolution computed tomography, endoscopy, and biopsy were performed as indicated. Cause of death was recorded from the death certificate.

Data Analysis

Data were analyzed using SPSS version 20 (IBM Corp). The Kolmogorov-Smirnov test was performed to evaluate the normality of distribution. Data are presented as mean (SD) if normally distributed and as median (range) if nonnormally distributed. A 1-way analysis of variance was used to investigate probable differences in quantitative variables between PAD groups. A post hoc analysis was performed using the Scheffe method to further evaluate the differences between pairs of PAD disorders. The chi-square or Fisher exact test was performed to evaluate differences in categorical variables between the PAD groups, as indicated. A linear regression analysis was used to determine the association between the date of onset of disease and diagnostic delay. Probabilities of survival after diagnosis of PAD were estimated using the Kaplan-Meier method.

Results

Patient Characteristics

The study population comprised 280 cases of PAD (209 male and 71 female) distributed as 125 CVID patients (44.6%), 63 SIgAD patients (22.5%), 60 XLA patients (21.4%), and 32 HIgM patients (11.4%). Four cases initially diagnosed as SIgAD later progressed to CVID. Median age was 16.5 (1-63) years. The median age of patients at onset of disease was 1 (0.01-46) year. By the age of 2 years, 46.4% of CVID patients, 52.3% of SIgAD patients, 75% of HIgM patients, and

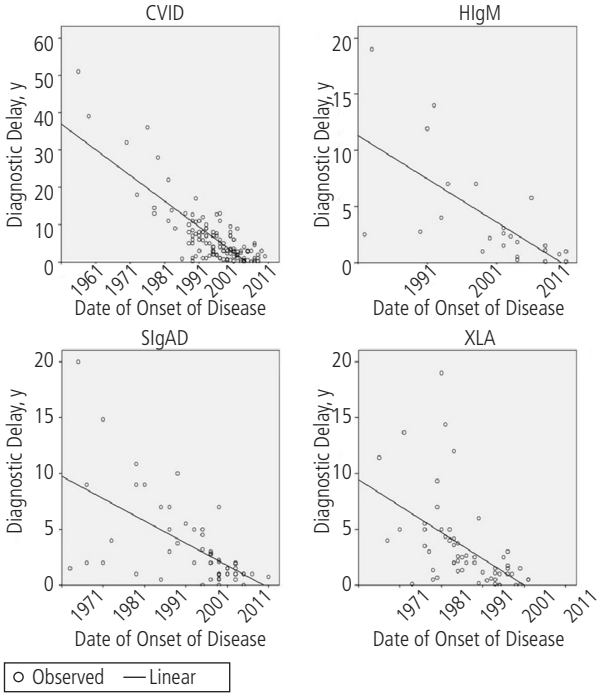

Figure 1. Association between the date of onset of disease and diagnostic delay in patients with common variable immunodeficiency (CVID), hyper IgM syndrome (HIgM), selective IgA deficiency (SIgAD), and X-linked agammaglobulinemia (XLA).

Table 1. Patients' Characteristics and Demographic Data

	CVID	HIgM	SIgAD	XLA	Total	*P* Value Between Groups	*P* Value CVID vs HIgM	*P* Value CVID vs SIgAD	*P* Value CVID vs XLA	*P* Value HIgM vs SIgAD	*P* Value HIgM vs XLA	*P* Value SIgAD vs XLA
Number (%)	125	32	63	60	280							
Sex, M/F	76/49	27/5	46/17	60/0	209/71	<.001[a]	.021[a]	.135	<.001[a]	.325	.004[a]	<.001[a]
Age, y	19.5 (4-63)	10.5 (2-36)	11 (5-36)	18.5 (1-40)	16.5 (1-63)	<.001[a]	.002[a]	<.001[a]	.077	.999	.363	.262
Age at onset, y	2 (0-46)	0.91 (0-9)	1 (0-26)	1 (0-10)	1 (0-46)	.007[a]	.101	.691	.03[a]	.591	1	.514
Age at diagnosis, y	8.25 (0-54)	3.75 (1-26)	6 (0-26)	3.88 (0-24)	6 (0-54)	<.001[a]	.041	.023[a]	<.001[a]	.987	.949	.723
Diagnostic delay, y	4 (0-51)	2.17 (2-19)	2 (0-20)	2 (0-19)	2.84 (0-51)	.002[a]	.276	.033	.021[a]	.995	.989	1

Abbreviations: CVID, common variable immunodeficiency; HIgM, hyper IgM syndrome; SIgAD, selective IgA deficiency; XLA, X-linked agammaglobulinemia.
[a]Statistically significant.

Table 2. Most Common First Clinical Manifestation at the Onset of Disease According to the Type of Primary Antibody Deficiency[a]

	CVID (n=125)	HIgM (n=32)	SIgAD (n=63)	XLA (n=60)	Total (n=280)	*P* Value Between Groups	*P* Value CVID vs HIgM	*P* Value CVID vs SIgAD	*P* Value CVID vs XLA	*P* Value HIgM vs SIgAD	*P* Value HIgM vs XLA	*P* Value SIgAD vs XLA
Respiratory tract infections	100 (80%)	32 (100%)	33 (52.4%)	32 (53.3%)	197 (70.4%)	<.001[b]	.002[b]	<.001[b]	<.001[b]	<.001[b]	<.001[b]	.915
Diarrhea	28 (22.4%)	7 (21.9%)	6 (9.5%)	13 (21.7%)	41 (14.6%)	.172	.949	.054	.91	.181	.981	.106
Allergy	3 (2.4%)	0 (0%)	12 (19%)	0 (0%)	12 (4.2%)	<.001[b]	1	<.001[b]	.552	.007[b]	1	<.001[b]

Abbreviations: CVID, common variable immunodeficiency; HIgM, hyper-IgM syndrome; SIgAD, selective IgA deficiency; XLA, X-linked agammaglobulinemia.
[a]Some patients might have had 2 or more clinical manifestations at the onset of disease. Manifestations observed in fewer than 10 cases are not shown.
[b]Statistically significant.

65% of XLA patients had experienced the first manifestation of disease, indicating earlier presentation of HIgM and XLA compared with CVID and SIgAD. By the age of 5 years, 69.6% of CVID patients, 73% of SIgAD patients, 81.2% of HIgM patients, and 86.6% of XLA patients had experienced the first manifestation of disease. While 4% of CVID patients and 3.1% of SIgAD patients experienced the first manifestation of disease after 18 years of age, all of the HIgM and XLA patients had their first manifestation before 10 years of age. The median age of the patients at the time of diagnosis was 6 (0.08-54) years. The median diagnostic delay was 2.83 (0-51) years. Patients were followed for a total of 1652 patient-years. The 1-way analysis of variance revealed a significant difference between the 4 types of PAD with respect to age, age at onset, age at diagnosis, and diagnostic delay. Patients with XLA had a significantly lower age at onset than patients with CVID (P=.03). Table 1 compares the characteristics and demographic data of CVID, HIgM, SIgAD, and XLA patients. There was a significant reverse association between the date of onset and diagnostic delay in all types of PAD (P<.001) (Figure 1). There were no significant differences between the 4 types of PAD for this association.

First Clinical Manifestation

Infections were the most common presenting feature of PAD at onset. Out of 280 patients, 251 (89.6%) experienced various types of infection as their first presentation of disease. As shown in Table 2, there were significant differences between various types of PAD for the prevalence of infection as the first manifestation of PAD (P=.005). More than 90% of patients with CVID, HIgM, and XLA experienced infectious manifestations at disease onset (92%, 93.8%, and 95% respectively). This rate was considerably lower in patients with SIgAD, of whom 22.2% experienced a noninfectious manifestation as the presenting feature of their disease (P<.001 for SIgAD vs CVID, HIgM, and XLA). Respiratory tract infection was the most common presenting feature (observed in 197 patients [70.4%]) followed by diarrhea (41 patients [14.6%]) and allergy (12 [4.2%]). Patients with SIgAD were significantly more likely to present with allergy than patients with other types of PAD (P<.001, P=0.007, and P<.001 for SIgAD vs CVID, HIgM, and XLA). Other manifestations were observed in fewer than 10 cases. Table 2 shows the most common presenting features of PAD for the different types of PAD.

Clinical Manifestations and Complications

Clinical manifestations and complications of PAD during the course of the disease included infection, autoimmunity, malignancy, enteropathy, allergy, and lymphoproliferative disorders.

Infectious complications were observed in all cases except 1 patient with SIgAD. Infections of the respiratory system were the most common (244 patients [87.1%]), followed by infections of the gastrointestinal tract (142 patients [50.7%]), skin (105 [37.5%]), skeletal system (37 [13.2%]), urinary tract (27 [9.6%]), and central nervous system (25 [8.9%]). Table 3 compares infections in various systems for these 4 PAD types.

Table 3. Comparison of Infections According to Type of Antibody Deficiency

	CVID (n=125)	HIgM (n=32)	SIgAD (n=63)	XLA (n=60)	Total	*P* Value Between Groups	*P* Value CVID vs HIgM	*P* Value CVID vs SIgAD	*P* Value CVID vs XLA	*P* Value HIgM vs SIgAD	*P* Value HIgM vs XLA	*P* Value SIgAD vs XLA
Respiratory, No. (%)	117 (93.6%)	29 (90.6%)	47 (74.6%)	51 (85%)	244 (87.1%)	.003[a]	.696	<.001[a]	.104	.101	.532	.227
Gastrointestinal, No. (%)	83 (66.4%)	16 (50%)	20 (31.7%)	23 (38.3%)	142 (50.7%)	<.001[a]	.131	<.001[a]	<.001[a]	.131	.391	.564
Cutaneous, No. (%)	48 (38.4%)	15 (46.9%)	15 (23.8%)	27 (45%)	105 (37.5%)	.048[a]	.389	.11	.351	.045[a]	.863	.025[a]
Central nervous system, No. (%)	13 (10.4%)	0	0	12 (20%)	25 (8.9%)	<.001[a]	.071	.005[a]	.119	1	.006[a]	<.001[a]
Skeletal system, No. (%)	19 (15.2%)	5 (15.6%)	2 (3.2%)	11 (18.3%)	37 (13.2%)	.047[a]	1	.013[a]	.108	.041[a]	1	.007[a]
Urinary tract, No. (%)	16 (12.8%)	3 (9.3%)	2 (3.2%)	2 (3.3%)	27 (9.6%)	.065	.766	.036[a]	.06	.331	.337	1
Multiple sites, No. (%)	103 (82.4%)	22 (68.8%)	15 (23.8%)	39 (65%)	179 (63.9%)	<.001[a]	.143	<.001[a]	.014[a]	<.001[a]	.895	<.001[a]

Abbreviations: CVID, common variable immunodeficiency; HIgM, hyper-IgM syndrome; SIgAD, selective IgA deficiency; XLA, X-linked agammaglobulinemia.
[a]Statistically significant.

Table 4. Comparison of Clinical Manifestations According to Type of Primary Antibody Deficiency

	CVID (n=125)	HIgM (n=32)	SIgAD (n=63)	XLA (n=60)	Total (n=280)	*P* Value Between Groups	*P* Value CVID vs HIgM	*P* Value CVID vs SIgAD	*P* Value CVID vs XLA	*P* Value HIgM vs SIgAD	*P* Value HIgM vs XLA	*P* Value SIgAD vs XLA
Infectious, No. (%)	124 (99.2%)	32 (100%)	58 (98.1%)	56 (93.3%)	270 (96.4%)	.028[a]	1	.016[a]	.038[a]	.163	.293	1
Autoimmunity, No. (%)	38 (30.4%)	13 (40.6%)	14 (22.2%)	11 (18.3%)	76 (27.1%)	.081	.373	.312	.118	.101	.131	.755
Malignancy, No. (%)	10 (8%)	1 (3.1%)	0	0	11 (3.9%)	.014[a]	.463	.032[a]	.031[a]	.336	.347	1
Enteropathy, No. (%)	22 (17.6%)	3 (9.4%)	15 (23.8%)	6 (10%)	46 (16.4%)	.133	.415	.414	.258	.104	.923	.072
Allergy, No. (%)	39 (31.2%)	6 (18.8%)	43 (68.3%)	10 (16.7%)	98 (35%)	<.001[a]	.241	<.001[a]	.055	<.001[a]	.801	<.001[a]
Lymphoproliferative, No. (%)	67 (53.6%)	21 (65.6%)	6 (9.5%)	15 (25%)	109 (38.9%)	<.001[a]	.306	<.001[a]	<.001[a]	<.001[a]	<.001[a]	.041[a]

Abbreviations: CVID, common variable immunodeficiency; HIgM, hyper-IgM syndrome; SIgAD, selective IgA deficiency; XLA, X-linked agammaglobulinemia.
[a]Statistically significant.

Table 5. Main Complications According to Type of Primary Antibody Deficiency

	CVID (n=125)	HIgM (n=32)	SIgAD (n=63)	XLA (n=60)	Total (n=280)	*P* Value Between Groups	*P* Value CVID vs HIgM	*P* Value CVID vs SIgAD	*P* Value CVID vs XLA	*P* Value HIgM vs SIgAD	*P* Value HIgM vs XLA	*P* Value SIgAD vs XLA
Bronchiectasis	43 (34.4%)	3 (9.3%)	1 (1.6%)	12 (20%)	59 (21.1%)	<.001[a]	.004[a]	<.001[a]	.066	.109	.308	.002[a]
Cirrhosis	3 (2.4%)	1 (3.1%)	1 (1.6%)	4 (6.6%)	9 (3.2%)	.376	1	1	.212	1	.654	.2
AIHA	5 (4%)	4 (12.4%)	0 (0%)	0 (0%)	9 (3.2%)	.004[a]	.084	.171	.176	.011[a]	.012[a]	1
JRA	3 (2.4%)	4 (12.5%)	0 (0%)	4 (6.6%)	11 (3.9%)	.013[a]	.032[a]	.552	.216	.011[a]	.442	.053
ITP	5 (4%)	5 (15.5%)	0 (0%)	3 (5%)	13 (4.6%)	.006[a]	.03[a]	.17	.715	.003[a]	.121	.113
Lymphadenopathy	44 (35.2%)	13 (40.6%)	3 (4.8%)	4 (6.6%)	64 (22.8%)	<.001[a]	.716	<.001[a]	<.001[a]	<.001[a]	<.001[a]	.715
Hepatomegaly	39 (31.2%)	9 (28.1%)	0 (0%)	11 (18.3%)	59 (21.1%)	<.001[a]	.903	<.001[a]	.095	<.001[a]	.412	<.001[a]
Splenomegaly	50 (40%)	11 (34.4%)	0 (0%)	7 (11.7%)	68 (24.3%)	<.001[a]	.704	<.001[a]	<.001[a]	<.001[a]	.019[a]	.005[a]
Enteropathy	26 (20.8%)	3 (9.3%)	5 (7.9%)	5 (8.3%)	39 (13.9%)	.03[a]	.201	.041[a]	.033[a]	1	1	.935
FTT	26 (20.8%)	6 (18.7%)	1 (1.6%)	4 (6.6%)	37 (13.2%)	<.001[a]	.797	<.001[a]	.018[a]	.005[a]	.09	.2

Abbreviations: AIHA, autoimmune hemolytic anemia; CVID, common variable immunodeficiency; FTT, failure to thrive; HIgM, hyper-IgM syndrome; ITP, immune (idiopathic) thrombocytopenia purpura; JRA, juvenile rheumatoid arthritis; SIgAD, selective IgA deficiency; XLA, X-linked agammaglobulinemia.
[a]Statistically significant.

Autoimmunity was observed in 76 patients (27.1%), enteropathy in 46 patients (16.4%), allergy in 98 patients (35%), and lymphoproliferative complications in 109 patients (38.9%). Allergic manifestations were observed in 43 SIgAD patients (68.3%), 39 CVID patients (31.2%), 6 HIgM patients (18.8%), and 9 XLA patients (15%). These manifestations were observed more significantly in SIgAD than in other types of PAD (P<.001 for SIgAD vs CVID, HIgM, and XLA). The most common allergic manifestation was drug reactions (24 PAD patients [8.6%]), followed by urticaria (20 [7.1%]), eczema (19 [6.8%]), asthma (15 [5.4%]), food allergy (12 [4.3%]), allergic rhinitis (11 [3.9%]), allergic conjunctivitis (10 [3.6%]), and atopic dermatitis (8 [2.9%]). Other allergic manifestations were observed in fewer than 5 cases. Tables 4 and 5 show the various types of clinical manifestations and complications among the 4 PAD types.

Malignancy

Malignancy was observed in 11 PAD patients (3.9%): 10 (8%) CVID patients and 1 (3.1%) HIgM patient (P=.461, .032, and .031 for CVID vs HIgM, SIgAD, and XLA, respectively). The 11 patients included 4 cases of CVID with non-Hodgkin lymphoma, 3 cases of CVID with gastric adenocarcinoma, 2 cases of CVID and 1 case of HIgM with Hodgkin lymphoma, and 1 case of CVID with breast cancer.

Mortality

Out of 280 PAD patients, 58 (20.7%) had died by the end of follow-up. A total of 107 patients (60.7%) were known to be alive, and 52 patients (18.6%) could not be located during the last 6 months of follow-up. No deaths were reported among patients with SIgAD. The mortality rate was not significantly different in patients with CVID, HIgM, and XLA (27.2%, 28.1%, and 25% respectively). The cause of death was respiratory failure in 19 cases, liver failure in 6 cases, cardiac arrest in 8 cases, septic shock in 6 cases, massive hemorrhage in 2 cases, gastric cancer in 2 cases, Hodgkin lymphoma in 2 cases, non-Hodgkin lymphoma in 1 case, Kawasaki disease in 1 case, encephalitis in 1 case, and meningitis in 1 case. The cause of death was unknown in 9 cases.

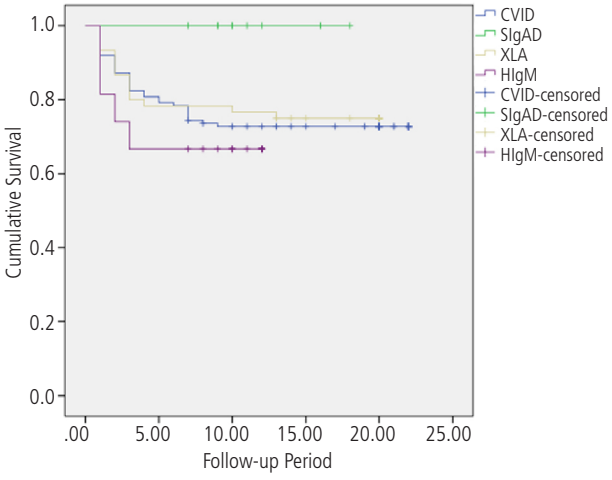

Figure 2. Survival Curve for Common Variable Immunodeficiency (CVID), Hyper-IgM Syndrome (HIgM), Selective IgA Deficiency (SIgAD), and X-Linked Agammaglobulinemia (XLA).

There were no significant differences in diagnostic delay between patients who died and patients who lived (4.59 [6.11] years vs 5.73 [7.21] years, P=.26). In contrast, the number of hospitalizations was significantly higher in patients who died (4.72 [2.17] vs 3.22 [3.39], P=.021). The number of episodes of infection was also significantly higher in patients who died (20.29 [17.19] vs 11.51 [11.75], P=.007).

No significant differences were found between patients who lived and patients who died in terms of consanguinity, family history of PID, family history of recurrent infections, family history of death at an early age, family history of malignancy, and family history of allergy. However, a family history of autoimmunity was more common in patients who lived (12.2% vs 0%, P=.025). Survival curves for CVID, SIgAD, HIgM, and XLA patients are presented in Figure 2. The log-rank test revealed significant differences in the survival only between SIgAD patients and the remaining 3 types of PAD (P<.001).

Discussion

We present the demographic and clinical data of 280 PAD patients diagnosed in a tertiary referral hospital over a 30-year period. CVID, which is the most symptomatic type of PAD [27], was the most prevalent type of PAD in the present study, affecting nearly half of the population. Although this finding contrasts with the results of European studies reporting SIgAD to be the most common type of PAD [28], it is consistent with the results of studies performed in Australia and Japan [29,30]. Most reported cases of SIgAD are asymptomatic, probably because studies from Asian countries, including the current study, are hospital-based and do not include asymptomatic cases [31].

In our study, the median age at disease onset was 1 year, and the median diagnostic delay was 2 years and 10 months. In a study on English PAD patients, the median age at onset was 41 years and the median diagnostic delay 2 years [32]. The higher prevalence of PAD among younger Iranian individuals may be a consequence of high rates of consanguineous marriages and a higher prevalence of autosomal recessive forms, especially among CVID patients [33-35]. Interestingly, XLA patients were still younger at disease onset than CVID patients, whose disease presented in childhood, thus pointing to probable clinical involvement in the diagnosis of patients with suspected PAD. Diagnostic delay in patients referred to our center was similar to that reported for European patients, indicating acceptable awareness among physicians and access to diagnostic methods at the Children's Medical Center hospital in Tehran, Iran [36].

Infection was the first sign of disease in about 90% of our study population. Infection is the most prominent clinical feature of all types of PAD [2,28]. Respiratory tract infection was the most prevalent manifestation at onset, followed by gastrointestinal tract infection, except for SIgAD patients, in

whom allergic complications were the second most prevalent initial manifestation after respiratory tract infection. Although the frequency of allergic disorders as the presenting feature of PAD has not been evaluated, a tendency toward allergy has been reported among SIgAD patients [16,37].

Infection was also the most common complication during the course of disease in our study population. All patients except for 1 SIgAD patient experienced at least 1 serious infection. Although it was reported that up to 90% of SIgAD patients are asymptomatic at onset, about 80% of these patients are predicted to experience infections or allergic and autoimmune disorders during the course of their disease [38]. Infections of the upper and lower respiratory tracts were the most common infectious complications in the current study. Respiratory tract infections were observed in 74% of patients with SIgAD, and in more than 85% of patients with CVID, HIgM, and XLA. Other authors report similar findings for the prevalence of respiratory tract infection in patients with CVID (76%) [22], HIgM (80%) [23], and XLA (85%) [39]. The prevalence of these infections among SIgAD patients in the present study was higher than reported by Macpherson et al [40], who found that most cases were asymptomatic, in contrast with the findings of the present study. However, almost all reports agree that respiratory tract infection is the most common type of infection among SIgAD patients [37,40].

Allergy was the most common noninfectious complication, especially in SIgAD patients, followed by autoimmunity, which was observed in 27% of patients. This finding is similar to that of Sarmiento et al [41], who reported autoimmunity in 23% of PAD patients. Malignancy was also a major complication in our study population and was observed most commonly among CVID patients. Consistent with this finding, Vajdic et al [29] evaluated the prevalence of malignancy among various types of PAD and found that CVID patients were at a much higher risk of developing cancer than other PAD patients.

The mortality rate in CVID, HIgM, and XLA was about 25% in our study population. No deaths were observed among SIgAD patients, consistent with reports of very low mortality due to complications of SIgAD [16]. The mortality rate in XLA patients was similar to that reported in 2 studies on the outcome of XLA published in 1985 and 1993 (17% and 25%, respectively) [42,43]. However, a study performed in 2002 on the outcome of Italian XLA patients showed a much lower mortality rate (1.4%) than the one we report here, indicating poor management of this disorder among Iranian XLA patients [44,45]. Cunningham-Rundles and Bodian [22] reported a mortality rate of 22% among American CVID patients, which is in agreement with the findings of the present study for a similar follow-up period. It is likely that the true mortality rate of our study population is higher than reported, since around 18% of patients could not be located during the last 6 months of the follow-up period [46].

The present study provides long-term follow-up and a valid comparison of the major types of PAD. However, several limitations should be addressed. First, genetic analysis is not routinely available in Iran, with the result that samples have to be sent overseas for evaluation of probable genetic defects. Hence, underlying molecular defects are not determined in most cases. Second, our hospital is a referral center for patients with suspected immunodeficiency in Iran, a Middle Eastern country with high rates of consanguineous marriages; therefore, its findings may not be a true reflection of PAD in other regions of the world. Third, since some patients were lost to follow-up, true mortality rates may be significantly different from those presented here.

In conclusion, observation of recurrent and/or severe infections as the most prevalent feature of PAD should lead the physician to suspect these disorders. Greater awareness facilitates timely diagnosis, which in turn decreases morbidity and mortality. Of the 4 most common types, SIgAD is more likely to become complicated by allergic and autoimmune conditions but less likely to be associated with severe and recurrent infections than other types of PAD. Patients with CVID are also at a much higher risk of malignancy than patients with other types of PAD.

Funding

This study was supported by a grant from Tehran University of Medical Sciences (Grant Number: 21651).

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Abolhassani H, Parvaneh N, Rezaei N, Hammarstrom L, Aghamohammadi A. Genetic defects in B-cell development and their clinical consequences. J Investig Allergol Clin Immunol. 2014;24:6-22; quiz 2 p following 22.
2. Durandy A, Kracker S, Fischer A. Primary antibody deficiencies. Nat Rev Immunol. 2013;13:519-33.
3. Aghamohammadi A, Allahverdi A, Abolhassani H, Moazzami K, Alizadeh H, Gharagozlou M, Kalantari N, Sajedi V, Shafiei A, Parvaneh N, Mohammadpour M, Karimi N, Sadaghiani MS, Rezaei N. Comparison of pulmonary diseases in common variable immunodeficiency and X-linked agammaglobulinaemia. Respirology. 2010;15:289-95.
4. Mamishi S, Eghbali AN, Rezaei N, Abolhassani H, Parvaneh N, Aghamohammadi A. A single center 14 years study of infectious complications leading to hospitalization of patients with primary antibody deficiencies. Braz J Infect Dis. 2010;14:351-5.
5. Abolhassani H, Aghamohammadi A, Imanzadeh A, Mohammadinejad P, Sadeghi B, Rezaei N. Malignancy phenotype in common variable immunodeficiency. J Investig Allergol Clin Immunol. 2012;22:133-4.
6. Abolhassani H, Amirkashani D, Parvaneh N, Mohammadinejad P, Gharib B, Shahinpour S, Hirbod-Mobarakeh A, Mirghorbani M, Movahedi M, Gharagozlou M, Rezaei N, Aghamohammadi A. Autoimmune phenotype in patients with common variable immunodeficiency. J Investig Allergol Clin Immunol. 2013;23:323-9.
7. Pan-Hammarstrom Q, Hammarstrom L. Antibody deficiency diseases. Eur J Immunol. 2008;38:327-33.
8. Conley ME, Broides A, Hernandez-Trujillo V, Howard V, Kanegane H, Miyawaki T, Shurtleff SA. Genetic analysis of

patients with defects in early B-cell development. Immunol Rev. 2005;203:216-34.
9. Minegishi Y, Rohrer J, Conley ME. Recent progress in the diagnosis and treatment of patients with defects in early B-cell development. Curr Opin Pediatr. 1999;11:528-32.
10. Aghamohammadi A, Fiorini M, Moin M, Parvaneh N, Teimourian S, Yeganeh M, Goffi F, Kanegane H, Amirzargar AA, Pourpak Z, Rezaei N, Salavati A, Pouladi N, Abdollahzade S, Notarangelo LD, Miyawaki T, Plebani A. Clinical, immunological and molecular characteristics of 37 Iranian patients with X-linked agammaglobulinemia. Int Arch Allergy Immunol. 2006;141:408-14.
11. Khalili A, Plebani A, Vitali M, Abolhassani H, Lougaris V, Mirminachi B, Rezaei N, Aghamohammadi A. Autosomal recessive agammaglobulinemia: a novel non-sense mutation in CD79a. J Clin Immunol. 2014;34:138-41.
12. Durandy A, Kracker S. Immunoglobulin class-switch recombination deficiencies. Arthritis Res Ther. 2012;14:218.
13. Aghamohammadi A, Parvaneh N, Rezaei N, Moazzami K, Kashef S, Abolhassani H, Imanzadeh A, Mohammadi J, Hammarstrom L. Clinical and laboratory findings in hyper-IgM syndrome with novel CD40L and AICDA mutations. J Clin Immunol. 2009;29:769-76.
14. Aghamohammadi A, Abolhassani H, Latif A, Tabassomi F, Shokuhfar T, Torabi Sagvand B, Shahinpour S, Mirminachi B, Parvaneh N, Movahedi M, Gharagozlou M, Sherkat R, Amin R, Aleyasin S, Faridhosseini R, Jabbari-Azad F, Cheraghi T, Eslamian MH, Khalili A, Kalantari N, Shafiei A, Dabbaghzade A, Khayatzadeh A, Ebrahimi M, Razavinejad D, Bazregari S, Ebrahimi M, Ghaffari J, Bemanian MH, Behniafard N, Kashef S, Mohammadzadeh I, Hammarstrom L, Rezaei N. Long-term evaluation of a historical cohort of Iranian common variable immunodeficiency patients. Expert Rev Clin Immunol. 2014;10:1405-17.
15. Aghamohammadi A, Farhoudi A, Moin M, Rezaei N, Kouhi A, Pourpak Z, Yaseri N, Movahedi M, Gharagozlou M, Zandieh F, Yazadni F, Arshi S, Mohammadzadeh I, Ghazi BM, Mahmoudi M, Tahaei S, Isaeian A. Clinical and immunological features of 65 Iranian patients with common variable immunodeficiency. Clin Diagn Lab Immunol. 2005;12:825-32.
16. Aghamohammadi A, Cheraghi T, Gharagozlou M, Movahedi M, Rezaei N, Yeganeh M, Parvaneh N, Abolhassani H, Pourpak Z, Moin M. IgA deficiency: correlation between clinical and immunological phenotypes. J Clin Immunol. 2009;29:130-6.
17. Saghafi S, Pourpak Z, Aghamohammadi A, Pourfathollah AA, Samadian A, Farghadan M, Attarchi Z, Zeidi M, Asgaripour F, Rajabi T, Kardar GA, Moin M. Selective immunoglobulin A deficiency in Iranian blood donors: prevalence, laboratory and clinical findings. Iran J Allergy Asthma Immunol. 2008;7:157-62.
18. Yel L. Selective IgA deficiency. J Clin Immunol. 2010;30:10-6.
19. Yong PF, Thaventhiran JE, Grimbacher B. "A rose is a rose is a rose," but CVID is Not CVID common variable immune deficiency (CVID), what do we know in 2011? Adv Immunol. 2011;111:47-107.
20. Aghamohammadi A, Mohammadi J, Parvaneh N, Rezaei N, Moin M, Espanol T, Hammarstrom L. Progression of selective IgA deficiency to common variable immunodeficiency. Int Arch Allergy Immunol. 2008;147:87-92.
21. Cheraghi T, Aghamohammadi A, Mirminachi B, Keihanian T, Hedayat E, Abolhassani H, Sagvand BT, Rezaei N. Prediction of the evolution of common variable immunodeficiency: HLA typing for patients with selective IgA deficiency. J Investig Allergol Clin Immunol. 2014;24:198-200.
22. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. Clin Immunol. 1999;92:34-48.
23. Winkelstein JA, Marino MC, Ochs H, Fuleihan R, Scholl PR, Geha R, Stiehm ER, Conley ME. The X-linked hyper-IgM syndrome: clinical and immunologic features of 79 patients. Medicine (Baltimore). 2003;82:373-84.
24. Nourijelyani K, Aghamohammadi A, Salehi Sadaghiani M, Behniafard N, Abolhassani H, Pourjabar S, Rezvanizadeh A, Khadamy J, Imanzaeh A, Sedaghat M, Rezaei N. Physicians awareness on primary immunodeficiency disorders in Iran. Iran J Allergy Asthma Immunol. 2012;11:57-64.
25. Ebadi M, Aghamohammadi A, Rezaei N. Primary immunodeficiencies: a decade of shifting paradigms, the current status and the emergence of cutting-edge therapies and diagnostics. Expert Rev Clin Immunol. 2015;11:117-39.
26. Conley ME, Notarangelo LD, Etzioni A. Diagnostic criteria for primary immunodeficiencies. Representing PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies). Clin Immunol. 1999;93:190-7.
27. Aghamohammadi A, Pouladi N, Parvaneh N, Yeganeh M, Movahedi M, Gharagolou M, Pourpak Z, Rezaei N, Salavati A, Abdollahzade S, Moin M. Mortality and morbidity in common variable immunodeficiency. J Trop Pediatr. 2007;53:32-8.
28. Salehzadeh M, Aghamohammadi A, Rezaei N. Evaluation of immunoglobulin levels and infection rate in patients with common variable immunodeficiency after immunoglobulin replacement therapy. J Microbiol Immunol Infect. 2010;43:11-7.
29. Vajdic CM, Mao L, van Leeuwen MT, Kirkpatrick P, Grulich AE, Riminton S. Are antibody deficiency disorders associated with a narrower range of cancers than other forms of immunodeficiency? Blood. 2010;116:1228-34.
30. Ishimura M, Takada H, Doi T, Imai K, Sasahara Y, Kanegane H, Nishikomori R, Morio T, Heike T, Kobayashi M, Ariga T, Tsuchiya S, Nonoyama S, Miyawaki T, Hara T. Nationwide survey of patients with primary immunodeficiency diseases in Japan. J Clin Immunol. 2011;31:968-76.
31. Rezaei N, Aghamohammadi A, Moin M, Pourpak Z, Movahedi M, Gharagozlou M, Atarod L, Ghazi BM, Isaeian A, Mahmoudi M, Abolmaali K, Mansouri D, Arshi S, Tarash NJ, Sherkat R, Akbari H, Amin R, Alborzi A, Kashef S, Farid R, Mohammadzadeh I, Shabestari MS, Nabavi M, Farhoudi A. Frequency and clinical manifestations of patients with primary immunodeficiency disorders in Iran: update from the Iranian Primary Immunodeficiency Registry. J Clin Immunol. 2006;26:519-32.
32. Seymour B, Miles J, Haeney M. Primary antibody deficiency and diagnostic delay. J Clin Pathol. 2005;58:546-7.
33. Rezaei N, Mohammadinejad P, Aghamohammadi A. The demographics of primary immunodeficiency diseases across the unique ethnic groups in Iran, and approaches to diagnosis and treatment. Ann N Y Acad Sci. 2011;1238:24-32.

34. Mohammadi J, Liu C, Aghamohammadi A, Bergbreiter A, Du L, Lu J, Rezaei N, Amirzargar AA, Moin M, Salzer U, Pan-Hammarstrom Q, Hammarstrom L. Novel mutations in TACI (TNFRSF13B) causing common variable immunodeficiency. J Clin Immunol. 2009;29:777-85.
35. Aghamohammadi A, Mohammadinejad P, Abolhassani H, Mirminachi B, Movahedi M, Gharagozlou M, Parvaneh N, Zeiaee V, Mirsaeed-Ghazi B, Chavoushzadeh Z, Mahdaviani A, Mansouri M, Yousefzadegan S, Sharifi B, Zandieh F, Hedayat E, Nadjafi A, Sherkat R, Shakerian B, Sadeghi-Shabestari M, Hosseini RF, Jabbari-Azad F, Ahanchian H, Behmanesh F, Zandkarimi M, Shirkani A, Cheraghi T, Fayezi A, Mohammadzadeh I, Amin R, Aleyasin S, Moghtaderi M, Ghaffari J, Arshi S, Javahertrash N, Nabavi M, Bemanian MH, Shafiei A, Kalantari N, Ahmadiafshar A, Khazaei HA, Atarod L, Rezaei N. Primary immunodeficiency disorders in Iran: update and new insights from the third report of the national registry. J Clin Immunol. 2014;34:478-90.
36. Mohammadinejad P, Mirminachi B, Sadeghi B, Movahedi M, Gharagozlou M, Mohammadi J, Abolhassani H, Rezaei N, Aghamohammadi A. Distribution of primary immunodeficiency disorders diagnosed in a tertiary referral center, tehran, iran (2006-2013). Iran J Immunol. 2014;11:282-91.
37. Janzi M, Kull I, Sjoberg R, Wan J, Melen E, Bayat N, Ostblom E, Pan-Hammarstrom Q, Nilsson P, Hammarstrom L. Selective IgA deficiency in early life: association to infections and allergic diseases during childhood. Clin Immunol. 2009;133:78-85.
38. Wang N, Hammarstrom L. IgA deficiency: what is new? Curr Opin Allergy Clin Immunol. 2012;12:602-8.
39. Lee PP, Chen TX, Jiang LP, Chan KW, Yang W, Lee BW, Chiang WC, Chen XY, Fok SF, Lee TL, Ho MH, Yang XQ, Lau YL. Clinical characteristics and genotype-phenotype correlation in 62 patients with X-linked agammaglobulinemia. J Clin Immunol. 2010;30:121-31.
40. Macpherson AJ, McCoy KD, Johansen FE, Brandtzaeg P. The immune geography of IgA induction and function. Mucosal Immunol. 2008;1:11-22.
41. Sarmiento E, Mora R, Rodriguez-Mahou M, Rodriguez-Molina J, Fernandez-Cruz E, Carbone J. Autoimmune disease in primary antibody deficiencies. Allergol Immunopathol (Madr). 2005;33: 69-73.
42. HermaszewskiRA,WebsterAD.Primaryhypogammaglobulinaemia: a survey of clinical manifestations and complications. Q J Med. 1993;86:31-42.
43. Lederman HM, Winkelstein JA. X-linked agammaglobulinemia: an analysis of 96 patients. Medicine (Baltimore). 1985;64:145-56.
44. Plebani A, Soresina A, Rondelli R, Amato GM, Azzari C, Cardinale F, Cazzola G, Consolini R, De Mattia D, Dell'Erba G, Duse M, Fiorini M, Martino S, Martire B, Masi M, Monafo V, Moschese V, Notarangelo LD, Orlandi P, Panei P, Pession A, Pietrogrande MC, Pignata C, Quinti I, Ragno V, Rossi P, Sciotto A, Stabile A. Clinical, immunological, and molecular analysis in a large cohort of patients with X-linked agammaglobulinemia: an Italian multicenter study. Clin Immunol. 2002;104:221-30.
45. Abolhassani H, Hirbod-Mobarakeh A, Shahinpour S, Panahi M, Mohammadinejad P, Mirminachi B, Shakari MS, Samavat B, Aghamohammadi A. Mortality and morbidity in patients with X-linked agammaglobulinaemia. Allergol Immunopathol (Madr). 2015;43:62-6.
46. Abolhassani H, Akbari F, Mirminachi B, Bazregari S, Hedayat E, Rezaei N, Aghamohammadi A. Morbidity and mortality of Iranian patients with hyper IgM syndrome: a clinical analysis. Iran J Immunol. 2014;11:123-33.

Manuscript received December 27, 2014; accepted for publication April 7, 2015.

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